Amendments to the Drawings:

Please replace the prior drawings with the enclosed formal replacement sheets.

REMARKS

Reconsideration of the present application, as amended, is respectfully requested. Claims 1-2 and 8-24 are pending and under prosecution.

AMENDMENTS TO THE SPECIFICATION

As required by the Examiner, a header for the "Brief Description of the Drawings" is now provided at page 23. As required by 37 C.F.R. §1.84(a)(2), a statement concerning the presence of color drawings in the application is inserted at page 24 of the application. In addition, the Brief Description of the Drawings is amended to conform to the labeling of the replacement drawing sheets, enclosed herewith, wherein the partial views are labeled with the abbreviation "FIG." pursuant to 37 C.F.R. §1.84 (u). Further, Figures 3 and 4, part "L)" respectively, are now labeled "FIG. 3J" and "FIG. 4J" respectively, pursuant to 37 C.F.R. §1.84 (u) so that the partial views of those figures are now labeled consecutively.

No new matter is added.

AMENDMENTS TO THE CLAIMS

Claim 1 is amended to address the several objections/rejections raised by the Examiner as to clarity and antecedent basis with in the claim, and to more closely conform to U.S. practice. Thus, as suggested by the Examiner, claim 1 step (b) now recites a "wherein" clause in place of a "based on the" phrase. Step (c) is amended for clarity and to recite that the "VH and VL regions" are "of the framework acceptors of human origin" and to spell out the acronym "RMS." Step (d) is amended to recite "a CDR region" to address the antecedent basis issue and to define the measurement of a root mean square deviation, as supported by the specification at. e.g., page 13, lines 3-22 and page 34, lines 21-23.

Claims 10, 15-17, 19, 21 and 23 are amended to more correctly recite "anti-TrkA" with a lower case "k" in conformity with the specification, e.g., at page 5, line 4.

No new matter is added.

AMENDMENTS TO THE DRAWINGS

Applicants submit herewith replacement drawing sheets that are now in formal compliance with U.S. practice. Thus, the replacement drawings have character size of 0.32 cm or larger, have text that is correctly oriented, and have Italian language text replaced with English language equivalents. Where appropriate, the drawing views are more clearly labeled. The subviews of Figures 3 and 4, formerly labeled as "L,", respectively, are now labeled as FIG. 3J AND 4J, respectively, to preserve consecutive numbering.

In addition to the submitted formal drawings, Applicants also enclose herewith a Petition under 37 C.F.R. § 1.84(a)(2) for permission to enter certain of the drawings in color. The color drawings are submitted, in triplicate, with the Petition, with payment of the required fee. Black and white copies of the color drawings are also enclosed herewith. The required amendment to the specification pursuant to 37 C.F.R. §1.84(a)(2) is also provided hereinabove.

The Examiner's courtesy in conducting a telephone interview with Applicants' undersigned representative, on December 3, 2010, is appreciated. The Examiner confirmed that color replacement drawings may be entered into the application with filing of the appropriate petition pursuant to 37 C.F.R. §1.84(a)(2), and payment of the petition fee. The Examiner further confirmed that the entry of drawing sheets in color would not be considered to be new matter, since the colors were referenced in the original specification.

No new matter is added.

OBJECTIONS TO THE DRAWINGS ARE OBVIATED

At item 6 of the Office Action, the Examiner has objected to the presence of references to colors in the Brief Description of the Drawings. Applicants have now submitted herewith replacement drawings, formalized, and a Petition To Request Acceptance of Color Drawings Pursuant to 37 C.F.R. §1.84(a)(2), as suggested by the Examiner. The enclosed replacement drawing sheets are also conformed to U.S. practice requirements, as discussed above.

For all of these reasons, this ground of objection or rejection is respectfully submitted to be obviated.

OBJECTION TO THE SPECIFICATION IS OBVIATED

At item 7 of the Office Action, the specification is objected to for not providing a heading for the "Brief Description of the Drawings."

It is respectfully submitted that the above-provided amendment to the specification obviates this ground of objection.

OBJECTIONS TO THE CLAIMS ARE OBVIATED

At item 8 of the Office Action, the claims are objected to for alleged informalities and an alleged lack of clarity. The Examiner's attention to this point is appreciated, and claim 1 has been amended to provide greater clarity and antecedent basis within that claim.

As noted above, as suggested by the Examiner, claim 1 step (b) now recites a "wherein" clause in place of a "based on the" phrase. Step (c) is amended for clarity and to recite that the "VH and VL regions" are "of the framework acceptors of human origin" and to spell out the acronym "RMS." Step (d) is amended to recite "a CDR region" to address the antecedent basis issue raised by the Examiner.

It is respectfully submitted that the above-provided amendments to claim 1 obviate this ground of objection.

THE CLAIMS ARE DEFINITE UNDER 35 USC § 112, SECOND PARAGRAPH

At item 10 of the Office Action, claims 1, 2 and 24 are rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite. The Examiner explains the alleged indefiniteness, as follows.

> Claim 1 is a method of *humanizing* the VH and VL regions of an animal antibody - that is, one skilled in the art inserts human sequences/regions *into* the animal antibody. However, the last step of claim 1 states it is the other way around, e.g. inserting in appropriate positions the sequence of animal antibodies *into* the human sequences or human antibodies, which results in doing the opposite of what the preamble suggests.

Applicants respectfully disagree. The Examiner's attention is respectfully directed to the amended preamble of claim 1, reciting "a process for producing a humanized antibody comprising VH and VL variable regions of an animal antibody of known sequence, comprising

the steps of..." Thus, claim 1 is now unambiguously consistent with the definition of a "humanized immunoglobulin" in the specification (e.g., page 8, lines 21-26) as mentioned by the Examiner.

It is submitted that claim 1 is both definite and clear as written. For all of these reasons, it is respectfully requested that this ground of rejection be reconsidered and withdrawn.

THE INVENTION

Applicants provide the following remarks, in order to clarify the nature and distinctiveness of their invention.

The invention provides a method for determining differences between animal and human antibodies by first making crystallographic measurements of the respective antibodies. Once the crystallographic structure is obtained for the subject antibodies, the invention requires:

i) primary sequence alignment and

ii) comparison of three-dimensional tertiary structures resolved at high resolution.

In particular, the method as claimed allows the selection of the optimal framework for antibody humanization (also see page 13, lines 25-33 and page 14, lines 1-4 of the present application). Previous humanization design procedures known to the art, are exceedingly cyclical and iterative, requiring many successive cycles of point mutations in the attempt to reconstitute the properties of the starting antibody, with a trial and error procedure that cannot be completely rationalized.

In contrast, the method of the claimed invention reduces the number of possible tertiary structures to be compared, limiting itself to those of human origin or humanized antibodies characterized by a high degree of homology and identity. Among these sequences characterized by an optimal alignment at the primary structure level and for which structural data are available, a further selection is conducted, concentrating only on the resolved structures with high resolution (i.e. no greater than 2.5Å). This approach assures a much more accurate alignment of the tertiary structures and much more significant estimates of the structural differences, expressed in root mean square deviation (RMS). In comparison, low resolution data provide only indicative and definitely less precise information on the actual relative position of each individual atom in space.

THE CLAIMS ARE NONOBVIOUS UNDER 35 USC § 103(a)

Claims 1, 2 and 24 are rejected under 35 U.S.C. § 103 as allegedly obvious over Queen et al. ("Queen;" US 5,693,761) taken in view of Ramsland et al. ("Ramsland;" *J. Mol. Recognition* 15: 248-259, 2002).

The Examiner takes the position that Queen teaches using human framework sequences that are closely homologous in linear peptide sequence, to framework sequences of the mouse antibody to be humanized. The Examiner concedes that Queen fails to teach that molecular models are determined by crystallographic methods, but cites the Ramsland reference to remedy this deficiency.

Ramsland is stated to teach "the comparison of crystal structures of humanized and mouse-human chimeric Fab antibodies (resolution 2.6A)." The Examiner also states that "in 2002 (the time of publication) there were more than 300 crystallographically determined antibody structures determined and found in the protein databank (PDB), 50 of those are different human immunoglobulins (see Introduction)." The Examiner then concluded that it would have been obvious to substitute the crystallographic comparison of Ramsland for the molecular comparison of Queen.

Applicants respectfully disagree. As noted above, the Examiner has conceded that Queen fails to teach the claimed method of conducting an interspecies comparison via high resolution X-ray crystallography. The Examiner then assumes, without any supporting evidence or technical reasons, that the claimed method would have been suggested to the artisan by the teachings of Queen taken with Ramsland.

The law requires that the claims must be considered as a whole, e.g., Manual of Patent Examining Procedure (MPEP) §2141.06(I). The MPEP explains that:

> In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983). [Emphasis in original].

The methods of claim 1, *et seq.*, require, in outline form:

a) obtaining a crystallographic structure of the VH and VL regions of the animal antibody; ...
b) pre-selecting a series of 0 to n possible framework acceptors of human origin or humanized antibodies, ...
c) conducting a structural comparison between the VH and VL variable regions of the animal antibody and the VH and VL regions of the framework receptors of human origin...and
- calculating for each comparison the root mean square deviation (RMS,Å), to identify the VH region and the VL region of human origin with the smaller RMS, in particular, the RMS is calculated between atoms of alpha carbon constituting the respective amino acid skeletons, not considering atom pairs with an RMS exceeding 2Å;
d) inserting in appropriate position a CDR region of the animal antibody into the VH region and the VL region of human origin identified in c).

Thus, claim 1 requires five specific steps [step (c) comprises two steps] and any rejection of claim 1 must meet the legal burden to show how the cited reference(s) would have taught or suggested all of these five process steps to obtaining a humanized antibody with a human or humanized framework and VH and VL regions from a desired animal antibody.

In contrast, Queen teaches an old method of "humanizing" an animal antibody by replacing the CDRs of the anti-Tac antibody with human framework and constant regions. On the other hand, the invention of claim 1, *et seq.*, provides a completely different method, where animal variable domains are inserted into a human or humanized antibody, while also employing an entirely different method of identifying the residues to be so inserted.

While Queen fails to teach anything about steps (a), (b), (c) and (d) for determining crystallographic comparisons between human and animal antibody structures, Ramsland fails to remedy these deficiencies. Ramsland describes, in general, the detailed structural information available for human antibodies with regard to their immune functions. Regarding the application of structural information in the humanization of antibodies, Ramsland is generic: "successful application of this knowledge has been made in the rapidly emerging field of antibody engineering, in the development of humanized antibodies for therapy of human disease" (p. 257, left column, first paragraph).

Ramsland only mentions one instance where crystallographic investigation was applied to two pre-existing antibodies, *i.e.* humanized AF2 and mouse-human chimeric AF2. That study was designed to understand why the humanized antibody had a two-fold lower affinity for its target when compared to the chimeric antibody (p. 255, right column, second paragraph). Hence,

Ramsland does not use crystal structures for the selection of frameworks for the humanization process, but describes *a posteriori* determination of the crystal structures of pre-existing humanized and chimeric antibodies in order to understand their characteristics. Thus Ramsland employs *a posteriori* structural information to rationalize the reasons why an already performed humanization led to loss of affinity/specificity of the humanized version. Thus, at best, Ramsland teaches about the failures of others in the field.

In contrast, the present invention teaches an *a priori* method that employs structural data for a structure-based framework selection. Neither Queen nor Ramsland, in any combination, would have taught the artisan the usefulness of crystal structures for the preselection of a series of possible framework acceptors to produce humanized antibodies. Further, Queen and Ramsland, in any combination, fails to teach or suggest the claimed method obtaining a humanized antibody by inserting animal antibody variable domains into a human antibody structure. Further still, Queen and Ramsland, taken in any combination, fail to teach or suggest how crystallographic data may be used in such a method. In addition, Queen and Ramsland, in any combination, fail to teach or suggest that only tertiary structures obtained with a resolution greater than 2.5 Å are to be used, and that the RMS must be calculated.

For all of these reasons, reconsideration and withdrawal of this ground of rejection is respectfully requested.

Claims 1, 2 and 24 are also rejected under 35 U.S.C. § 103 as allegedly obvious over Pedersen et al. ("Pedersen;" US5,639,641) in view of Ramsland et al. (as above). The Examiner takes the position that Pedersen teaches humanizing a rodent antibody by resurfacing the antibody by, "comparing framework sequences between species" and that "[t]he human variable domain with the highest percentage [identity to the mouse sequence] is selected to provide the framework sequences for the humanizing project, citing to Cols. 5-6 of Pedersen. The Examiner concedes that Pedersen fails to teach that molecular models are determined by crystallographic methods, but cites Ramsland, as above, to remedy this deficiency.

Applicants respectfully disagree. As explained above, the methods of claim 1, *et seq.*, requires five specific steps for preparing a humanized antibody according to the invention. These are steps (a), (b), (c) and (d) as enumerated above, wherein (c) includes two process steps.

The deficiencies of Queen as a reference against the claimed invention are discussed above. Pederson fails to remedy these clear deficiencies. Pederson merely teaches another old

method of trying to produce a humanized antibody starting with an animal i.e., murine antibody. Pederson teaches a method of "resurfacing" a murine antibody by replacing surface exposed (environmentally exposed) amino acid residues with human-form analogues, e.g., by the method summarized from Col. 5, line 23 through Col. 6, line 23 of Pederson. Pederson nowhere would have taught or suggested to the artisan that the method of Queen could be modified to produce the method as recited by claim 1. Further, tn Queen and Pederson, a murine antibody is modified to appear more antigenically human. In the claimed invention, a human antibody is modified to include the binding specificity of an animal, i.e., murine variable domain, thus operating in the reverse direction from that which is taught by the cited references.

Further, Queen and Pederson, taken in any combination, fail to teach or suggest the claimed method obtaining a humanized antibody by inserting animal antibody variable domains into a human antibody structure. Further still, Queen and Pederson, taken in any combination, fail to teach or suggest how crystallographic data may be used in such a method. In addition, Queen and Pederson, in any combination, fail to teach or suggest that only tertiary structures obtained with a resolution greater than 2.5 Å are to be used, and that the RMS must be calculated.

For all of these reasons, reconsideration and withdrawal of this ground of rejection is respectfully requested.

Applicants have also considered the Tamura and Harris et al. references made of record and not relied on by the Examiner. Applicants submit that these references are no more pertinent than those relied on by the Examiner, and reserve the right to traverse any future rejection based on one or both of these references.

NON-STATUTORY OBVIOUSNESS-TYPE DOUBLE PATENTING

The Examiner has *provisionally* rejected claims 1, 2 and 24 as allegedly obviousness-type double patenting over claims 1, 2 and 24 of copending Appl. Ser. No. 12/838,062. Since this rejection is provisional, because neither patent application has been allowed, Applicants respectfully reserve the right to respond to this provisional ground of rejection once there is an indication of allowable subject matter in the instant patent application.

CONCLUSION

It is respectfully submitted that application is in condition for allowance, and reconsideration and allowance is hereby requested. If any questions remain, the Examiner is respectfully requested to contact the undersigned for a telephone interview, in the interest of expeditious prosecution.

FEES

No fees are believed to be owed for entry of this Response. Nevertheless, if it is determined that any fees are due or any overpayment has been made, the Assistant Commissioner is hereby authorized to debit or credit such sum to Deposit Account No. 02-2275.

A Petition for Extension of Time for One-Month, is enclosed herewith, together with the fee required for a Small Entity. Nevertheless, if further extension is required, pursuant to 37 C.F.R. 1.136(a)(3), please treat this and any concurrent or future reply in this application that requires a petition for an extension of time for its timely submission as incorporating a petition for extension of time for the appropriate length of time. The fee associated therewith is to be charged to Deposit Account No. 02-2275.

Should any additional fees or extensions of time be necessary in order to maintain this Application in pending condition, appropriate requests are hereby made and authorization is given to Deposit Account No. 02-2275.

CERTIFICATE
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on December 23, 2010.
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